Administration of Proton Pump Inhibitors In Patients Requiring Enteral Nutrition

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INTRODUCTION

Role of Proton Pump Inhibitors

Patients requiring enteral nutrition may also be in need of acid-suppressing therapy with proton pump inhibitors (PPIs). Currently, five PPIs are available in the U.S.: omeprazole (Prilosec, AstraZeneca), omeprazole/sodium bicarbonate (Zegerid, Santarus), esomeprazole (Nexium, AstraZeneca), lansoprazole (Prevacid, Tap/Takeda), pantoprazole (Protonix, Wyeth), and rabeprazole (Aciphex, Eisai). All of these products are available in oral form, and several are also available in an intravenous (IV) form (Table 1).[1]

PPIs are highly effective for the treatment of gastroesophageal reflux disease (GERD), ulcers, and gastrointestinal (GI) bleeding. Indications approved by the FDA for each PPI are provided in Table 1.

When gastric contents are at a pH of below 2, protein denaturation and the conversion of pepsinogen to pepsin occur and can lead to irritation of the esophagus.[2] Other factors such as histamine and gastrin also play a role in the secretion of gastric acid with resulting esophageal irritation.[3] Gastric contents at a pH of less than 4 for extended periods of time have been associated with a higher severity of disease. Therefore, it is not surprising that time spent at a pH above 4 has been correlated with esophageal healing.[2]

PPIs exhibit their effects by inhibiting H^+/K^+-adenosine triphosphatase (ATPase) in parietal cells.[2,3] This inhibition sufficiently raises and maintains gastric pH to exceed 4.[2] Currently available PPIs can maintain this pH level 50% to 60% of the time.[2]

Tube Feedings

Patients who require enteral nutrition may be supported by one of the following insertion techniques: nasogastric tube, nasoduodenal tube, gastrostomy tube, jejunostomy tube, or a combined gastrojejunostomy tube.[4] The use of feeding tubes to administer medications is common practice, but the procedure is complicated by the potential for the medication to clog or to adhere to the sides of the tube.

Although several PPIs are available in an IV form (see Table 1), if a patient has a functional GI tract, it may still be feasible to administer an oral formulation. The use of IV PPIs may also be complicated by a lack of venous access and cost restrictions. Administration of the capsule's contents via a feeding tube is further complicated by the fact that unless the PPI molecule is protected, it is subject to degradation in the presence of stomach acid.[3] The PPIs (except for Zegerid) are therefore encapsulated or enterically coated to prevent premature activation of the drug in the presence of gastric acid.[2,3] Opening the capsule and administering the contents have the potential to leave the granules vulnerable to degradation, premature activation, and decreased efficacy.

Information about administering PPIs via enteral feeding tubes is limited. This article discusses the available literature and provides practitioners with suitable methods of administering PPIs via nasogastric, gastrostomy, and jejunostomy tubes. A search of PubMed utilizing the terms omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole, enteral, nasogastric, gastrostomy, and jejunal was conducted. All retrievable *in vitro* and *in vivo* studies describing an extemporaneous formulation administered via an enteral tube were included for review.

NASOGASTRIC TUBES

Many PPIs include instructions in the package insert for administration via nasogastric tubes.[5–10] Table 2 presents enteral tube instructions for omeprazole delayed-release oral suspension packets, omeprazole/sodium bicarbonate powder for suspension, lansoprazole (Prevacid Solu-Tab), pantoprazole for delayed-release oral suspension, and esomeprazole delayed-release capsules and oral suspensions. Although the use of capsule contents is not documented in the package insert, they have been evaluated in various formulations for use via an enteral feeding tube.

Available in both capsule and suspension forms, Zegerid contains an antacid component in addition to a PPI component. The capsules, however, should not be opened.[8] If Zegerid is to be used, the powder for suspension should be prescribed.

Several studies have sought to determine the bioavailability and efficacy of many of these formulations via the enteral route and have also compared them with capsule and IV formulations. When considering agents to include on an institutional formulary, P&T committee members may be influenced by a drug's bioavailability and comparative efficacy.

A review of the literature describing enteral administration is provided next. Table 3 includes instructions on compounding the formulations used in the following studies.

Omeprazole Delayed-Release Capsules

Larson et al.[11]

In one of the earliest studies of omeprazole given by nasogastric tube, the agent's efficacy and bioavailability were sim-

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ilar in oral administration. Larson et al. enrolled 10 healthy volunteers who were taking no other medications. Acid output was measured in 15-minute intervals over one hour. Peak acid output was determined to be the sum of the highest two consecutive measurements. In this crossover study, oral administration decreased peak acid output by 85%, compared with 79.6% via nasogastric tube. The difference was not significant ($P = 0.30$).

Philips et al.[12]

Omeprazole given in a sodium bicarbonate solution has been shown to prevent stress-related mucosal bleeding and to raise GI pH in critically ill patients. Phillips et al. evaluated 75 patients on mechanical ventilation who received an omeprazole suspension until mucosal bleeding prophylaxis was no longer necessary. These patients received two doses of 40 mg, then a daily dose of 20 mg. Five patients had pre-existing GI bleeding, which resolved within 36 hours in all five. Of the 65 patients who received omeprazole as prophylaxis, none experienced GI bleeding. The mean baseline pH was 3.5 ± 1.9; after omeprazole therapy, the mean pH rose to 7.1 ± 1.1.

Tuleu et al.[13]

A case report by Tuleu et al. demonstrated the potential lack of efficacy of omeprazole in the pediatric population. An infant underwent routine stomach aspiration, which was performed 18 hours after the last omeprazole dose was given. The nurse noticed that the contents contained a poppy seed–like substance. The authors reported that this phenomenon had also occurred in at least six other infants. Upon high-performance liquid chromatography (HPLC) mass spectroscopy, the "poppy seeds" were discovered to be omeprazole and its degradation products. The authors speculated that the premature degrading was possibly caused by delayed gastric emptying and by the use of water instead of sodium bicarbonate to make a solution. Sodium bicarbonate is often used for suspensions to protect the PPI molecule from premature degradation; however, for these patients in pediatric intensive care, sodium bicarbonate was not used because of ventilator exposure and potential chronic alkalosis.

Haizlip et al.[14]

In a larger study of an omeprazole suspension in 18 critically ill pediatric patients, continuous gastric pH monitoring was used to determine efficacy. Patients were given the suspension at a dose of 1 mg/kg of body weight with titrations, as necessary, to a maximum of 20 mg. At the completion of the study, patients were classified according to their response to therapy. Patients were considered rapid responders if a goal pH of between 4 and 7 was maintained for most of the 12 hours after

Table I **Formulations of Proton Pump Inhibitors (PPIs) Available in the U.S.**

PPI	Capsule or Tablet	Solution or Granules for Oral Suspension	IV	FDA-Approved Indications
Omeprazole	Yes; capsule (prescription); tablet (over the counter)	Yes	No	Duodenal ulcer, *H. pylori* (combined with amoxicillin and/or clarithromycin), gastric ulcer, GERD, maintenance healing of erosive esophagitis, hypersecretory conditions
Omeprazole/ sodium bicarbonate	Yes; immediate-release capsule	Yes	No	Duodenal ulcer, gastric ulcer, GERD, maintenance healing of erosive esophagitis, upper GI bleeding risk reduction in critically ill patients
Esomeprazole	Yes; capsule	Yes	Yes	GERD, NSAID-associated gastric ulcer risk reduction, *H. pylori* eradication (in combination with amoxicillin and clarithromycin), hypersecretory conditions
Lansoprazole	Yes; capsule, disintegrating tablet	Yes	Yes	Duodenal ulcer, *H. pylori* eradication (combined with clarithromycin and/or amoxicillin), maintenance of healed duodenal ulcers, active benign gastric ulcer, healing of and risk reduction of NSAID-associated gastric ulcer, GERD, maintenance healing of erosive esophagitis, hypersecretory conditions
Pantoprazole	Yes; tablet	Yes	Yes	GERD-associated erosive esophagitis, maintenance healing of erosive esophagitis, hypersecretory conditions
Rabeprazole	Yes; tablet	No	No	Healing or maintenance of erosive or ulcerative GERD, GERD, duodenal ulcers, *H. pylori* (combined with amoxicillin and clarithromycin), hypersecretory conditions

* All oral formulations are delayed-release unless otherwise denoted.

GERD = gastroesophageal reflux disease; GI = gastrointestinal; *H. pylori* = *Helicobacter pylori* infection; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug.

Data from Lexi-Drugs[1] and package inserts for Nexium,[5] Prevacid,[6] Prilosec,[7] Zegerid,[8] Protonix,[9] and Aciphex.[10]

Table 2 Nasogastric Administration of Proton Pump Inhibitors (PPIs) as Suggested by Manufacturers

PPI	Instructions
Esomeprazole	*Delayed-release capsules* 1. Empty intact granules into a 60-mL catheter-tipped syringe. 2. Mix with 50 mL of water. 3. Replace plunger; vigorously shake for 15 seconds. 4. Check for granules in the syringe tip; if none, attach syringe and administer contents. 5. Flush tube with water. 6. Do *not* administer if granules have dissolved or have disintegrated. 7. Administer immediately after preparation. *Delayed-release oral suspension* 1. Add 15 mL of water to a catheter-tipped syringe. 2. Empty contents of packet into syringe (10, 20, or 40 mg). 3. Shake syringe; allow 2–3 minutes for suspension to thicken. 4. Shake syringe again and administer. 5. Draw 15 mL of water into syringe; shake and flush tube. 6. Administer in a French size 8 tube or larger. 7. Administer within 30 minutes of preparation.
Lansoprazole Solu-Tab	1. Place tablet in syringe; draw up correct amount of water (15 mg = 4 mL; 30 mg = 10 mL) 2. Gently shake. 3. Administer via tube within 15 minutes. 4. Refill syringe with 5 mL of water; flush tube.
Omeprazole delayed-release oral suspension packets	1. Add appropriate amount of water to a catheter-tipped syringe; add contents of packet (2.5 mg = 5 mL; 10 mg = 15 mL). 2. Shake syringe; allow 2–3 minutes for suspension to thicken. 3. Shake syringe again; administer contents. 4. Refill syringe with an equal amount of water to flush tube. 5. Administer in a French size 6 tube or larger. 6. Administer within 30 minutes of preparation.
Omeprazole and sodium bicarbonate powder for suspension	1. Constitute suspension in 20 mL of water. 2. Stir well. 3. Using a syringe, administer immediately. 4. Flush tube with 20 mL of water.
Pantoprazole delayed-release oral suspension packets	1. Remove plunger from 60-mL catheter-tipped syringe; attach syringe to tube. 2. Empty packet contents into syringe. 3. Add 10 mL of apple juice. 4. Gently shake syringe to empty contents into tube. 5. Flush syringe and tubing with 10 mL of apple juice. 6. Repeat flush at least two additional times or until no granules remain in syringe. 7. Administer in a French size 16 tube or larger. 8. Hold tubing upright during administration to prevent bending of tube.
Rabeprazole	No information available.

Data from package inserts for Nexium,[5] Prevacid,[6] Prilosec,[7] Zegerid,[8] Protonix,[9] and Aciphex.[10]

the first omeprazole dose (78 ± 25%).[14] Nine patients (50%), were classified as late or nonresponders; these patients maintained a goal pH of only 43 ± 19% and 20 ± 25% of the time during the 12 hours after the first omeprazole dose.

In addition to the disadvantage of an open-label study with a small number of participants, the authors stated other limitations that might have resulted in such a high failure rate. Differences in patient populations, premature activation of omeprazole, and a lack of pharmacokinetic evaluations further limited this study.

Olsen et al.[15]

Conversely, omeprazole has been quite effective in pediatric transplant patients. Omeprazole suspension was given via nasogastric tube in 11 postoperative patients who had undergone liver or intestinal transplantation (or both). Evaluated outcomes included changes in pH, time spent at a pH above 4, and pharmacokinetic and pharmacodynamic parameters. Patients received omeprazole 0.5 mg/kg twice daily, for a maximum of 20 mg. Continuous pH monitoring indicated that the baseline pH was 1.0 ± 0.8. After omeprazole was administered, the mean

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Table 3 **Alternative Methods of Enteral Tube Administration of Proton Pump Inhibitors (PPIs): Recipes and Efficacy**

Study	Tube	PPI	Recipe	Efficacy
Larson et al.[11]	Nasogastric	Omeprazole	1. Remove granules from capsule; place in small cup. 2. Flush 6–10 granules at a time with 10–20 mL of water.	No differences in reduction of acid output compared with capsule.
Phillips et al.[12]	Nasogastric	Omeprazole	1. Remove granules from capsule; place in empty 10-mL syringe with plunger removed. 2. Replace plunger; draw 8.4% sodium bicarbonate solution into syringe (10 mL for 20 mg; 20 mL for 40 mg) 3. Allow about 30 minutes for granules to dissolve; agitation is helpful. 4. Shake before use; do not administer with acidic substances.	Reduced bleeding associated with stress-related mucosal damage; effective in raising baseline pH.
Tuleu et al.[13]	Nasogastric	Omeprazole	10 mg of omeprazole in 10 mL of water used.	Case report of critically ill pediatric patient; degradation product found in stomach aspirate.
Haizlip et al.[14]	Nasogastric	Omeprazole	See recipe by Phillips et al.[31]	50% of critically ill pediatric patients experienced late or no response.
Olsen et al.[15]	Nasogastric	Omeprazole	1. Add granules of a 20-mg capsule to 10 mL of 8.4% sodium bicarbonate solution. 2. Allow 15–30 minutes for granules to dissolve; gently agitate. 3. Administer via tube; flush with water; clamp tubing for 30–60 minutes.	Effectively raised and maintained baseline pH; C_{max} and AUC greater after multiple dosing intervals.
Kaufman et al.[16]	Nasogastric	Omeprazole	An 8.4% sodium bicarbonate solution was used.	Effectively raised and maintained baseline pH.
Dunn et al.[17]	Nasogastric	Omeprazole Lansoprazole	1. Remove granules from capsule; place in small cup. 2. Mix with 30 mL of tap water, 15 mL of tap water, or 15 mL of apple juice. 3. Attach 60-mL catheter-tipped syringe with plunger removed to tube. 4. Flush tube with water (10 or 15 mL) or apple juice (15 mL). 5. Place dispersion into syringe; replace plunger (maintain 5 mL of air between plunger and dispersion). 6. Administer dispersion over 10–15 seconds. 7. Remove plunger. 8. Rinse cup with 10 or 15 mL of liquid; administer remaining granules. 9. Flush tube with 10 or 15 mL of liquid.	*In vitro* administration resulted in variable delivery rates; dispersion vehicle or volume did not affect delivery rates; size 14 French tube was used.
Chun et al.[18]	Nasogastric	Lansoprazole	1. Empty contents of a 30-mg capsule into 60-mL catheter-tipped syringe with plunger removed. 2. Add apple juice to syringe; replace plunger. 3. Remove all air from syringe; draw apple juice into syringe to make 40 mL. 4. Gently shake syringe. 5. Administer contents over 3–5 minutes. 6. Flush tube with 40 mL of apple juice; repeat once. 7. Total volume of apple juice to be used = 120 mL.	No differences in pharmacokinetic parameters when compared with capsule; size 16 French tube was used.

Table 3 **Alternative Methods of Enteral Tube Administration of Proton Pump Inhibitors (PPIs): Recipes and Efficacy** *continued*

Study	Tube	PPI	Recipe	Efficacy
Doan et al.[19]	Nasogastric	Lansoprazole	1. Place contents of 30-mg capsule in 10 mL of 8.4% sodium bicarbonate solution. 2. Administer immediately after preparation. 3. Flush tube with 30 mL of water.	Suspension was bioequivalent to capsule; size 8 French tube was used.
Freston et al.[20]	Nasogastric	Lansoprazole	1. Empty contents of 30-mg capsule into 60-mL catheter-tipped syringe. 2. Draw 40 mL of apple juice into syringe. 3. Gently mix. 4. Administer contents through tube by tilting and gently tapping syringe. 5. Flush tube with 40 mL of apple juice; repeat once. 6. Total volume of apple juice to be used = 120 mL.	Efficacy was maintained and produced similar effects as IV pantoprazole; size 16 French tube was used.
Tsai et al.[22]	Nasogastric	Lansoprazole	1. Insert ¼ of 30-mg capsule contents into syringe. 2. Add water; slowly administer granules. 3. Repeat until all granules are administered. 4. Flush tube with 15 mL of water.	Effectively reduced gastric acidity in critically ill patients; size 16 French tube or larger was used.
Ferron et al.[23]	Nasogastric	Pantoprazole	1. Grind 40-mg tablet into fine powder. 2. Transfer powder to glass container. 3. Rinse mortar and pestle with 5 mL of 4.2% sodium bicarbonate solution; repeat once; add obtained suspension to glass container. 4. Mix contents of glass container for 10 minutes until suspension forms. 5. Transfer suspension to polypropylene syringe. 6. Rinse glass container with 5 mL of 4.2% sodium bicarbonate solution; repeat once; add obtained suspension to syringe. 7. Administer contents; flush tube with 20 mL of water.	C_{max} is comparable to that of tablet; bioavailability of suspension is 25% lower than that of tablet; size 16 French tube used; may prepare suspension 4 hours before administration; protect from light.
Shah et al.[28]	Nasogastric gastrostomy	Esomeprazole	*Tap water suspension* 1. Add 25 mL of tap water to catheter-tipped syringe. 2. Empty contents of 40-mg capsule into syringe. 3. Replace syringe plunger; with syringe tip up, shake gently until all pellets move throughout the syringe (approx. 15 seconds). 4. Leaving 5 mL of air between plunger and contents, administer contents using a side-to-side shaking method if necessary. 5. Add 25 mL of tap water to syringe; shake vigorously for 15 seconds, and flush tube. *30% Ora-Plus Suspension* 1. Add 17.5 mL of tap water to catheter-tipped syringe. 2. Empty contents of 40-mg capsule into syringe. 3. Draw 30% Ora-Plus suspension into syringe until 25-mL mark is reached. 4. Replace syringe plunger; with the syringe tip up, shake gently until all pellets move throughout syringe (approx. 15 seconds). 5. Leaving 5 mL of air between plunger and contents, administer contents using a side-to-side shaking method if necessary. 6. Add 25 mL of tap water to syringe; shake vigorously for 15 seconds, and flush tube.	*In vitro* administration resulted in delivery rates of about 99%.

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Table 3 **Alternative Methods of Enteral Tube Administration of Proton Pump Inhibitors (PPIs): Recipes and Efficacy** *continued*

Study	Tube	PPI	Recipe	Efficacy
Sharma et al.[24]	Gastrostomy	Omeprazole	1. Flush tube with 15 mL of orange juice. 2. Empty contents of capsule into syringe. 3. Administer contents of syringe using small amounts of orange juice until all granules are administered. 4. Flush tube with 15 mL of orange juice.	Effective in raising baseline pH and in maintaining therapeutic pH for most of a 24-hour period.
Sharma et al.[25]	Gastrostomy	Omeprazole	1. Place contents of 20-mg capsule into 15-mL syringe. 2. Draw 10 mL of 8.4% sodium bicarbonate solution into syringe. 3. Gently shake for 10–15 minutes until white suspension forms. 4. Administer; flush tube with 10–15 mL of tap water.	Effective in raising baseline pH.
Sharma et al.[26]	Gastrostomy	Lansoprazole	1. Empty contents of 30-mg capsule into a 30-mL catheter-tipped syringe. 2. Add 1.5 fluid ounces of orange juice to administer granules. 3. Flush tube with an additional 1.5 fluid ounces of orange juice.	Effective in raising baseline pH.
Sharma et al.[27]	Gastrostomy	Lansoprazole	1. Empty contents of 30-mg capsule into 15-mL syringe. 2. Draw 10 mL of 8.4% sodium bicarbonate into syringe. 3. Gently shake for 10–15 minutes until granules dissolve and a white suspension forms. 4. Administer immediately; flush tube with 10–15 mL of tap water.	Effective in raising baseline pH.
White et al.[30]	Gastrostomy	Esomeprazole	1. Empty contents of capsule into 60-mL catheter-tipped syringe. 2. Add 50 mL of water. 3. Replace plunger, leaving 5 mL of air between liquid and plunger. 4. Shake syringe until all pellets move throughout syringe. 5. Shake syringe vigorously from front to back for 15 seconds. 6. Attach to tube; administer contents over 30 seconds; use gentle side-to-side shaking.	*In vitro* administration resulted in delivery rate of approx. 99%.
Phillips et al.[31]	Jejunal	Omeprazole	1. Dissolve contents of two 20-mg capsules in 20 mL of 8.4% sodium bicarbonate solution. 2. Gently shake to ensure mixing. 3. Administer contents; flush tube with 10 mL of water.	Higher C_{max}.; faster T_{max} compared with nasogastric administration; effective at raising and maintaining pH of less than 4.

AUC = area under the curve; C_{max} = maximum concentration; T_{max} = time of maximum concentration.

pH remained above 4 and was maintained at this level for 97.8% ± 5.4% of the time after multiple dosage intervals. Mean maximum concentration (C_{max}) and area-under-the-curve (AUC) values were significantly greater after multiple dosing intervals compared with the first dosing interval, as follows:

C_{max} initial = 812 ± 409.1 vs. C_{max} multiple = 1,258.7 ± 286.2 ($P < 0.05$)

AUC initial = 4,956.3 ± 3,305.4 vs. AUC multiple = 7,622.9 ± 2,738 ($P < 0.05$)

Kaufman et al.[16]

In another study of 22 liver and/or intestinal transplant pediatric patients, omeprazole was effective in suppressing gastric pH. Patients received omeprazole 0.5 mg/kg twice daily. Measured outcomes were gastric pH and the percentage of time spent with the pH above 4. Baseline pH, after the initiation of therapy, did not differ between patients undergoing liver transplantation (6.2 ± 0.5) or intestinal transplantation (6.1 ± 0.4). In addition, the time spent with the pH above 4 did not differ between liver transplant patients (86% ± 7%) and intestinal transplant patients (81% ± 8%). Finally, the time spent with the

pH above 4 correlated well with the mean pH for all 22 patients (r = 0.84).

Dunn et al.[17]

As seen in these studies, concerns remain about the administration of capsule contents and the premature activation of the PPI molecule, particularly when patients are compromised by delayed gastric emptying and by limitations to the use of sodium bicarbonate as a protective agent. Therefore, the vehicle in which the granules are administered is of equal importance.

Dunn and colleagues sought to determine whether omeprazole differed from lansoprazole in the number of granules delivered and whether water or apple juice served as a better vehicle of delivery. The investigators chose apple juice as a delivery medium because it was recommended by lansoprazole's manufacturer and because some studies indicated that acidic fruit juices would maintain the composition of omeprazole for up to 30 minutes.

This *in vitro* study also compared how well 15 mL, compared with 30 mL, of the liquid vehicle delivered the medication granules. The investigators individually counted the contents of each capsule and then mixed them with either 30 mL of water or with 15 mL of water or apple juice. A nasogastric tube was placed in a position similar to what it would be in a supine patient. The medication was administered through the tube and collected by a filter at the end. Two investigators recounted the granules. Approximately 50% of omeprazole granules and approximately 30% of the lansoprazole granules were delivered; this result was not found to be statistically significant ($P > 0.05$). However, when counts exceeding a 95% delivery were excluded, delivery rates did differ significantly between the two medications (approximately 45% for omeprazole vs. approximately 15% for lansoprazole; $P = 0.01$). Delivery rates were not affected by the amount or type of vehicle used.

Lansoprazole

Chun et al.[18]

As demonstrated in the *in vitro* study by Dunn et al., the administration of lansoprazole granules via nasogastric tube resulted in a very low delivery rate.[17] However, a small study by Chun et al. estimated that the number of granules that adhered to tubing was minimal (2% or less). In this crossover study, 23 healthy male volunteers were given an intact lansoprazole capsule and lansoprazole granules in apple juice. The primary objective was to determine differences in bioavailability. After evaluating pharmacokinetic parameters, the authors noted no significant difference between the capsule and granule formulations in their times to maximum concentration (T_{max}), peak concentration (C_{max}), half-life, or AUC concentration. The AUC point estimate fell within the 90% confidence interval (CI), indicating that the two formulations were bioequivalent (1.044, 90% CI, 0.955–1.140).

Doan et al.[19]

A second study of 36 healthy volunteers revealed similar results. The Doan study also had a crossover design, but a sodium bicarbonate suspension was used to deliver the lansoprazole granules. Significant differences were found between several pharmacokinetic parameters (T_{max}, C_{max}, and AUC); however, the C_{max} and AUC point estimates fell within the 90% CIs that determined bioequivalence (1.136, 90% CI, 1.037–1.244, and 0.851, 90% CI, 0.806–0.898, respectively). Because the capsule and suspension formulations were found to be bioequivalent, the differences noted in individual parameters are likely to be of limited clinical significance.

Freston et al.[20]

Freston et al. completed a comparative study of lansoprazole dispersion in apple juice given via nasogastric tube with IV pantoprazole. This crossover study compared pharmacokinetic and intragastric pH on the first and fifth days of treatment. This trial again demonstrated that the bioavailability of lansoprazole was not affected when it was given in an alternative form.

On the first day of treatment, patients receiving lansoprazole had a significantly higher mean pH than those treated with pantoprazole at 0 to 5 hours ($P = 0.0.29$), at 6 to 10 hours ($P = 0.001$), and at 11 to 15 hours ($P = 0.016$). The percentage of time spent above a pH of 3, 4, and 5 was also significantly higher in the lansoprazole group ($P < 0.001$ for all).

On day five of treatment, only the mean pH at the 6- to 10-hour segment and the 11- to 15-hour segment remained significantly higher for lansoprazole ($P = 0.004$ and $P = 0.048$, respectively). As for the percentage of time spent at a determined pH, only a pH above 3 for patients treated with lansoprazole remained significant ($P < 0.05$).

The authors pointed out several limiting factors that apply to all of the studies described thus far. Each study involved healthy, primarily male patients. From the literature, it is difficult to determine whether bioavailability and efficacy would remain the same in different patient populations. Freston et al. mentioned that PPIs were administered only once daily and that the effects on pH might be different with an increased frequency.

Olsen and Devlin[21]; Tsai et al.[22]

Two trials have demonstrated the efficacy of nasogastric administration in critically ill patients.[21,22]

Olsen and Devlin administered lansoprazole orally disintegrating tablets, according to package insert instructions, and compared them with IV lansoprazole. They found that the bioavailability of enterally administered lansoprazole was lower than that of the IV formulation, but its acid-suppressing ability was greater.[21]

Another study involving 15 critically ill patients documented similar results. Tsai et al. evaluated gastric pH and the percentage of time spent above a pH of 4 when lansoprazole granules were administered in water.[22] The median pH was significantly higher on the second and third days ($P = 0.001$), and the percentage of time spent above a pH of 4 was significantly higher on these days when compared with baseline values (76% and 84%, respectively, $P = 0.001$).[22]

Because water was used as the delivery medium, a concern was raised about exposure of the lansoprazole granules to stomach acid with a resulting premature activation of the drug. The Tsai study potentially circumvented this event by

including patients who tolerated tube feedings and by excluding patients with delayed gastric emptying or ileus.[22] The appropriate functioning and motility of the GI tract in these patients might have allowed for the timely passage of the medication into the small bowel.

Pantoprazole

Ferron et al.[23]

Although current manufacturer recommendations are available for administering pantoprazole oral suspension packets, none exist for the tablet.[9] Ferron et al. sought to compare the bioavailability of pantoprazole tablets with that of an oral suspension administered via a nasogastric tube (see Table 3). This crossover trial included 12 healthy males. A pharmacokinetic analysis found that although the C_{max} was similar for both formulations, the bioavailability was significantly lower for the suspension: tablet AUC = 6.53; suspension AUC = 4.89 ($P < 0.001$).

The authors noted that the reduced bioavailability might have been caused by the lower concentration of sodium bicarbonate used (i.e., 4.2% vs. 8.4% used for other PPIs), thus allowing for premature activation of the medication.

GASTROSTOMY TUBES

Omeprazole

Various formulations of omeprazole have been evaluated for administration via gastrostomy tubes.

Sharma et al.[24,25]

Sharma et al. evaluated omeprazole given by gastrostomy tube using intact granules suspended in orange juice.[24] In this open-label study, 14 male patients received 20 mg of omeprazole for seven days. Mean baseline 24-hour intragastric pH was 1.8, which rose to 4.9 after seven days of therapy with the omeprazole suspension ($P < 0.0001$). The proportion of time the intragastric pH was above 3 was also measured during the baseline and post-therapy 24-hour periods. At baseline, the mean time at a pH above 3 was 21%; after treatment, this proportion rose to 80% ($P < 0.0001$).[24]

In another study, Sharma and other colleagues also evaluated the use of a simplified omeprazole suspension (omeprazole granules suspended in sodium bicarbonate) in a similar patient population.[25] This open-label study was much smaller, with only six patients, and consisted of only male patients treated with 20 mg of omeprazole for seven days. The mean baseline 24-hour intragastric pH was 2.2 and rose to 4.1 after seven days of the omeprazole suspension ($P < 0.01$). The authors also measured the proportion of time during which the intragastric pH was above 3, 4, and 5 during the baseline and post-therapy 24-hour periods. At the baseline examination, the proportions of time during which patients' pH was above 3, 4, and 5 were 35%, 28%, and 17%, respectively. After treatment, these values rose to 63%, 51%, and 39% for a pH above 3, 4, and 5, respectively ($P < 0.05$).

A second phase of this trial included a liquid antacid in addition to omeprazole. After a seven-day treatment period, the antacid provided no additional benefit when compared with omeprazole alone ($P > 0.05$).[25]

Lansoprazole

Sharma et al.[26,27]

Sharma and colleagues also studied the effect of lansoprazole on pH when the drug was suspended in orange juice.[26] Using an identical study design as in the other trials just described,[24,25] the investigators found that lansoprazole was effective as a suspension in orange juice. Eight men received lansoprazole 30 mg for seven days. The mean 24-hour baseline pH was 1.9, which rose to 4.7 after therapy was completed ($P < 0.0001$). At the baseline evaluation, the proportion of time spent at a pH above 3, 4, and 5 was 23%, 13.5%, and 7.5%, respectively. After treatment, time proportions at a pH above 3, 4, and 5 rose to 81%, 70%, and 52%, respectively ($P < 0.0001$).[26]

In an open-label study, Sharma and associates also assessed the use of a simplified lansoprazole suspension administered by gastrostomy tube.[27] This study compared lansoprazole suspended in orange juice with a solution of lansoprazole made with sodium bicarbonate in six male patients. The patients first received lansoprazole in orange juice for seven days, followed by a lansoprazole suspension for seven days. The mean 24-hour baseline pH of 1.8 rose to 4.5 after seven days of lansoprazole in orange juice and to 5.1 after seven days of the suspension. Significant changes were found for each formulation compared with baseline ($P < 0.001$ for both); however, no significant differences were found between the two lansoprazole formulations themselves ($P > 0.05$).

The proportion of time at a pH exceeding 3, 4, and 5 also differed significantly for both formulations compared with baseline ($P < 0.01$); however, the formulations did not differ from each other ($P > 0.05$).[27]

Esomeprazole

Several *in vitro* studies have examined the delivery of esomeprazole pellets via nasogastric and gastrostomy tubes.

Shah et al.[28]; Johnson[29]

Shah et al. compared delivery of esomeprazole magnesium enteric-coated pellets in tap water with various concentrations of the suspension liquid, Ora-Plus (Paddock Laboratories),[28] a vehicle used for extemporaneous compounds.[29] In the first phase of the study, the authors used size 14 French standard nasogastric tubes to deliver esomeprazole pellets in tap water (Ora-Plus 30%, Ora-Plus 50%, and Ora-Plus 70%). After phase 1, pellet retention was significantly greater with Ora-Plus 70% ($P < 0.003$) than with the other vehicles.[28] Tap water and Ora-Plus 30% showed the least amount of retention and were therefore used for phase 2 of the study.

For phase 2, the authors used size 8 French nasogastric and size 20 French gastrostomy tubes. No differences were found between tap water and Ora-Plus 30% for either the nasogastric tubes ($P > 0.280$) or the gastrostomy tubes ($P > 0.886$).

During both phases, all methods were successful in delivering the dispersed pellets at a rate of 99%; however, during phase 2, one trial was excluded from analysis because of exceptionally large pellet retention with the use of tap water in a size 8 French nasogastric tube. The authors attributed this effect to the ever-present potential for clogging when drugs are given by a feeding tube.[28]

White et al.[30]

One additional *in vitro* study sought to determine whether the method of delivery or bore size affected the delivery rate of esomeprazole pellets. White et al. evaluated two sizes of nasogastric tubes and a size 20 French gastrostomy tube. They used current manufacturer guidelines for nasogastric administration; therefore, results for only the gastrostomy tube are reviewed here.

The authors tested delivery methods tested by administering medication in one or two steps. However, they tested the gastrostomy tube by only the one-step method, noting that almost 99% of pellets were delivered via gastrostomy tubing. No significant differences were observed between gastrostomy tubes and size 14 French nasogastric tubing.

Jejunostomy

Phillips et al.[31]

Published studies describing the administration of PPIs via a jejunostomy tube are exceedingly limited. Only one study was available. Phillips et al. evaluated pharmacokinetic parameters and gastric pH using omeprazole suspension in nine critically ill surgical patients in the intensive-care unit. The authors found that the T_{max} was significantly lower with the jejunal route (12.1 minutes) than with nasogastric administration (108.3 minutes) ($P < 0.001$). The C_{max} was also significantly higher with jejunal tubing (1.833 mcg/mL) than with nasogastric administration (0.970 mcg/mL) ($P = 0.0006$).

Although these two pharmacokinetic parameters did differ, the bioavailability of each administration route did not, indicating only limited to no clinical significance for the kinetic differences seen. Baseline pH rose from 1.63 to greater than 4 throughout the study period for patients who received omeprazole via the jejunal route. However, over a 24-hour period, jejunal administration resulted in a significantly lower mean pH when compared with nasogastric administration (5.57 vs. 6.32, respectively; $P = 0.015$).

CONCLUSION

Selecting agents to be included on an institutional formulary can be a daunting task for P&T committee members, particularly when several agents in a class exist with multiple formulations. PPI administration to hospitalized patients is a daily occurrence; therefore, the selection of one agent to include on the formulary is likely to be the most cost effective. When choosing an appropriate agent to interchange for the class, one would hope to ensure similar efficacy with the lowest cost possible and the flexibility to administer the medication in special populations.

Almost all PPIs may be given in some form via a nasogastric tube. Care must be taken to ensure that medications do not adhere to or clog the tubing. Health care professionals must consider many factors when administering a PPI via nasogastric tubing. Most frequently, the size of the tubing's diameter, the pellets, or the granules can affect the procedure; however, in populations such as the critically ill or pediatric patients, factors such as volume and sodium status must be considered as well.

Only three PPIs for delivery by gastrostomy tubes have been reported in the literature to support either their efficacy or their potential to be retained in the tubing. For jejunostomy tubes, only omeprazole has been studied. All administration methods cited in this article are listed in Table 3 along with a summary of their efficacy or bioavailability.

When giving PPIs via a nasogastric tube, health care professionals should follow all manufacturer recommendations regarding preparation and administration (see Table 2). Care should be taken with children and adolescents, because nasogastric administration has not been consistently found to be highly effective except for liver and intestinal transplant patients.

Omeprazole and lansoprazole have been effective when they are administered via gastrostomy tube. *In vitro* data suggest that esomeprazole may be a suitable option as well. For patients with a jejunostomy tube, only omeprazole has been effective.

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